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(54) Title: BONE CEMENT INCLUDING A CELL GROWTH STIMULANT

(57) Abstract

A bone cement, comprising a physiologically acceptable reaction resin, such as a PMMA casting resin mixture, and a cell growth stimulant, such as human growth hormone, is useful for healing bone fractures and repairing bone defects. The cement will promote bone cell formation and give joints having increased strength.

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BONE CEMENT INCLUDING A CELL GROWTH STIMULANT

The present invention relates to a bone cement which is useful for healing bone fractures, repairing bone defects and stablisation of prosthetic implants.

It is conventional to use bone cement in the fixation of prosthesis to bone in joint replacement surgery. One of the main problems associated with joint replacement using conventional bone cement, such as polymethylmethacrylate (PMMA) is aseptic loosening which is generally related to failure at the bone-cement interface. Post-operative changes occur at the bone-cement interface which can lead to a gap occurring between the bone and the cement. Eventually remodelling of the bone occurs. Any stimulus to remodelling or improvement in the quality of the bone-cement interface would be a distinct advantage in cemented joint replacement.

It is also normal practice to use a physiologically acceptable cement in healing fractured bones. The cement is applied to the fractured surfaces so that the fractured bones are kept in correct position until the healing process is finished and the fracture has grown together.

The cement may be mixed with antibiotics, such as Gentamicin, in order to avoid infections.

It has also been suggested to incorporate a bone morphogenetic protein (BMP) in the cement in order to induce formation of new bone in viable tissue, cf. US P No. 4 526 909. In the specification of this patent is disclosed a PMMA bone cement containing BMP. The composition may be supplemented with other agents as desired, such as fillers and antibiotics.

It is known that the protein BMP stimulates differentiation of connective tissue into bone cells, i.e. stimulate cartilage cells to turn into bone cells.

The present invention is based on the discovery that growth hormone stimulates proliferation of bone cells by increasing the level of IGF1 in the "target" cells, and that this effect causes the bone cells to multiply, grow, produce matrix and penetrate into the cement phase.

According to the present invention there is provided a bone cement, comprising a combination of physiologically acceptable reaction resin and a cell growth stimulant, preferably selected from the group consisting of somatotropins, somatomedines, parathyroid hormone (PTH), vitamin D and sex steroids.

Useful cell growth stimulants may be selected from the following groups:

1. Bone derived bone factors
2. Local regulators of bone metabolism
3. Growth regulator hormones
4. Calcium regulating hormones
5. Bone proteins

More specific examples of useful cell growth stimulants are:

	PREDOMINANT EFFECTS ON RESORPTION	ON FORMATION
<u>Calcium-regulating hormones</u>		
Parathyroid hormone	+	+
1,25-dihydroxyvitamin D	+	-, (+)
Calcitonin	-	0
<u>Systemic hormones</u>		
Growth hormone	0	(+)
Glucocorticoide	(+)	-
Thyroid hormones	+	+
Insulin	0	+
Estrogens	(-)	(-)
<u>Local factors</u>		
Prostaglandin E_2	+	+
Interleukin-1	+	-, (+)
Interferon-	-	-
Insulin-line growth factor 1	0	+
Transforming growth factor-b	-, (+)	+

The preferred cell growth stimulant to be used in the invention is human growth hormone (hGH). It has been shown that hGH, when it is incorporated in the cement, will increase the rate of healing of a bone fracture considerably and give a joint of increased strength.

The term "reaction resin" is used in the present concept to designate any casting resin in fluid, semi-liquid dough-like or mouldable form, capable of being cured or hardened at the temperature of application, usually between 30°C and 45°C, to form a strong, hard or flexible solid.

A preferred reaction resin is a polymerizing resin, such as a mixture of monomeric methyl methacrylate and powdered polymethyl methacrylate. This composition also

contains a catalyst and an accelerator. Examples of other useful resins are unsaturated polyesters or other liquid or mouldable polymerizing unsaturated compounds. Still other examples are ceramics and biodegradable organic galss.

Instead, a polycondensation resin can be used, such as a liquid high viscosity epoxy resin or a mixture of a di- or tri-isocyanate and a di- or triol, producing a polyurethane resin. Some polyurethane formulations will give a foamed resin, having increased flexibility and a high loading capacity for growth hormone or a similar cell growth stimulant.

In order to reduce the shrinking of the reaction resin during the curing process it can be mixed with a filler, such as Plaster of Paris or inorganic pigments or fibres. Also other additives, conventionally used in the plastics field, may be added.

According to a specific embodiment of the invention, the reaction resin may be a monomeric cyano acrylate. This material will polymerize very fast at a hydrophilic surface to a solid having a high bonding strength.

Used in total hip replacement surgery, the incorporation of hGH or a similar cell growth stimulant will result in increased bone remodelling and bone formation at the cement surface, leading to increased strength at the bone-cement interface. There is reduced risk of aseptic loosening and improved life time of the prosthesis.

The cement of the invention can be used in knee, elbow and schoulder replacement surgery or in small joint replacement, such as fingers, wrists or toes.

Instead of incorporating the hGH in the cement mixture,

the hGH can be applied to the bone-cement interface using supplying means, such as drainage tubes. For example, a bone fracture can be treated in the usual way using a plastic foam. A drainage tube could be inserted and after operation a solution of hGH could be introduced to the cement through the drainage tube at a controlled rate.

The cement loaded with hGH can also be used to fill and repair bone defects and osteotomies. The release of hGH from the material can lead to new bone cell formation in these areas. This application may require the use of a biodegradable polymer loaded with hGH-growth factors. The release of hGH will cause increased bone cell formation, the biodegradable polymer will eventually be resorbed and the defect will be filled with new bone.

hGH-loaded resin, such as PMMA, can be used to repair bone fractures, give joint increased strength and cause increased bone remodelling in conjunction with devices such a a plate, screw or intermedullary pin.

The invention will be further described with reference to the following examples and the drawings, considered illustrative but not limiting of the invention.

EXAMPLE 1

A material was made from the following substances:

Powder polymethylmethacrylate polymer 20 g
Liquid methylmethacrylate monomer 10 ml
Sterilized human growth hormone (Lypophilised powder) 6 mg

To make the material, the sterile human growth hormone in powder form was added to the powder polymer component

of PMMA bone cement and mixed thoroughly. The liquid monomer component was then added to the mixture and mixed using a plastics spatula until a "dough-like" consistency was formed. The material was then inserted into a previously prepared bone cavity.

The growth hormone loaded cement was implanted into one femur of adult sandy lop rabbits, with plain cement in the contralateral femur as a control. One month after surgery, the rabbits were sacrificed and the bone-cement interface examined using transmission electronmicroscopy. In the plain cement the zirconium dioxide (radiopague agent) could be seen in discreet pockets and the cement appeared clear (Fig. 1). In the growth hormone loaded cement, some invasion of the cement surface could be seen and new mineral deposited in the cement (Fig. 1). These findings were confirmed using X-ray microanalysis, and the spectra for growth hormone loaded cement gave calcium and phosporous peaks (Fig. 3), whereas spectra for the plain cement gave no calcium and phosphorous peaks (Fig. 4). These findings indicate that certain appropriate changes occur at the bone-cement interface when growth hormone loaded cement is used <u>in vivo</u>.

EXAMPLE 2

<u>Animal Study Using Growth Hormone Loaded PMMA</u>

In order to examine the <u>in vivo</u> effects of the use of growth hormone loaded cement, on the cement/bone interface, an animal model was employed.

Adult New Zealand White Rabbits between 2.5 kg and 5 kg were used. Under sterile conditions one vial human growth hormone (4.1 U) was added to each 10 gram pack of PMMA polymer component of Palacos bone cement. The cement was mixed as described above and inserted into

a 10 ml sterile syringe before insertion into the knee.

A medial parapatellar incision was made and access to the knee patella was dislocated laterally to expose the intercondylar area. Using 4 mm diameter drill bit the femoral medullary cavity was reamed to depth of 2 cm. Approximately 0.5 ml of cement was injected into each knee. On one side the cement was loaded with growth hormone (see above); plain cement was injected into the contralaterial femur to act as a control. Further controls were used where both femura received plain PMMA cement. The patellae were reduced and wounds closed with sutures. Post-operatively rabbits were kept unrestrained in sized cagoes (40 x 40 x 01).

The rabbits were divided into three groups which were sacrificed using an overdose of Euthatal (100 mg in 5 ml) after 1 month, 2 mohths and 4 months, respectively. The femora were removed and processed for histology.

<u>Histology of the Bone-Cement Interface</u>

The sections were prepared to include undecalcified bone and intact bone cement making it possible to examine the bone-cement interface intact. Examination of the histology sections revealed that viable bone was growing in direct contact with the PMMA bone cement. When considering PMMA as a drug delivery system it is important to establish whether the "target" tissue was in contact with the cement, this was clearly the case.

Electronmicroscopy studies revealed that viable bone cells were growing in direct contact with the growth hormone loaded cement.

One month after surgery:
The bone-cement interface was found to be composed of

between 14-21% mineralised bone, 28-52% osteoid bone and 41-60% cells. In all cases the knee containing growth hormone loaded PMMA contained a higher percentage of osteoid at the bone-cement interface than in the knee containing plain bone cement. This was statistically significant (P<0.01).

At two and four months the difference between the hGH loaded and plain cement interface became gradually less.

Findings

1. Viable bone cells grow along the cement surface and any GH released will reach the "target" bone cells.

2. Blood vessels are seen in the mineralised bone close to the cement interface - therefore remodelling of the bone can be expected.

3. Remodelling of the bone occurs over a period of 4 months after surgery.

4. A significantly higher percentage of osteoid is formed at the hGH loaded cement interface, one month after surgery, as compared with the control knees containing unloaded cement. The healing is accelerated.

The results of this preliminary trial indicate that there was an early response of the osteoblast cells to growth hormone, resulting in increased formation of osteoid one month after implanting the cement. These findings may be important because early stimulation of bone remodelling will bring skeletal cells and matrix to the cement surface thus strengthening the bond at the bone-cement interface.

The *in vivo* results of the rabbits experiments may be

important to the problem of aseptic loosening. The precise mechanism of early loosening is not fully understood, but it has been postulated that the primary cause is the shrinkage of cement in the bone cavity and accompanying bone necrosis. Under such circumstances, it would initiate a rapid synthetic response following prosthetic replacement. This was clearly seen in the growth hormone loaded cement series when analysed after one month.

P a t e n t C l a i m s :

1. A bone cement, comprising a combination of a physiologically acceptable reaction resin and a cell growth stimulant, selected from the group consisting of somatotropins, somatomedines, parathyroid hormone (PTH), vitamin D and sex steroids.

2. A cement according to claim 1, wherein the cell growth stimulant is human growth hormone (hGH).

3. A cement according to claim 1, wherein the reaction resin is a liquid or mouldable polymerizing casting resin.

4. A cement according to claim 1, wherein the reaction resin is a liquid or mouldable polycondensation resin.

5. A cement according to claim 1, wherein the reaction resin is a foam-forming mouldable mixture.

6. A cement according to claim 1, wherein the reaction resin is a monomeric cyano acrylate.

7. A cement according to claim 1 and 2, comprising a) a monomeric acrylic compound, and b) a mixture of powdered polymethylmethacrylate, human growth hormone and optionally fillers, pigments, catalysts, accelerators and other usual components.

8. A cement according to claim 5, also comprising means for supplying a growth stimulant containing solution to the moulded foam.

9. A method of joining bone surfaces to each other or to a prosthesis, wherein a combination of a reaction resin and a cell growth stimulant, selected from the

group consisting of somatotropins, somatomedins, parathyroid hormone (PTH), vitamin D and sex steroids, is applied to the surfaces to be joined, whereafter the reaction resin is cured while the surfaces are in intimate contact with each other.

11. A method of reparing bone defects, wherein a combination of a reaction resin and a growth stimulant, selected from the group consisting of somatotropins, somatomedins, parathyroid hormone (PTH), vitamin D and sex steroids, is applied to the defective parts of the bone and cured.

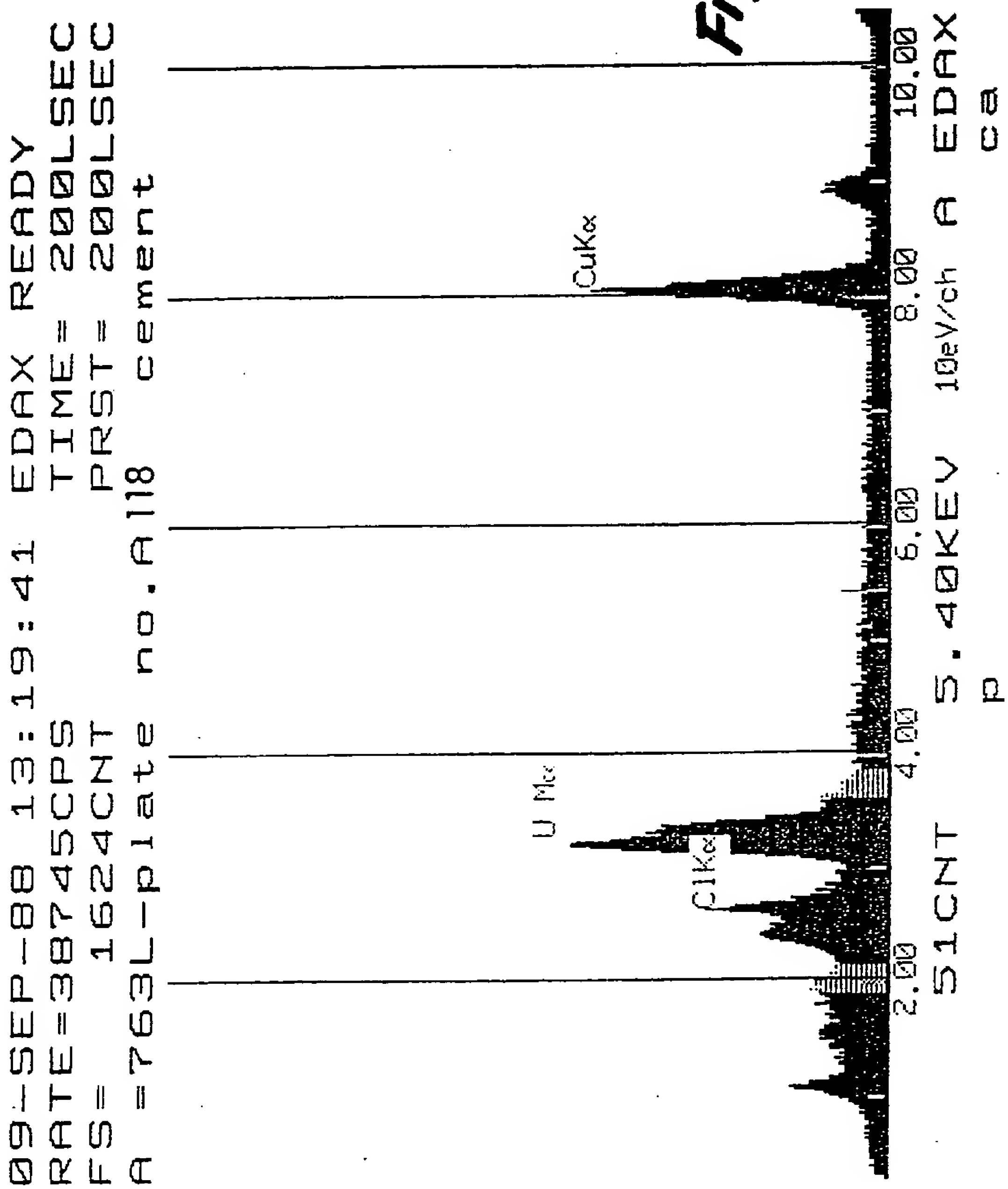
12. A method according to claim 10 or 11, wherein the combination consists of a monomeric acrylic compound and a mixture of powdered polymethylmethacrylate, catalysts, accelerators, fillers or other usual additives, and human growth hormone.

13. A bone cement, comprising a combination of a physiologically acceptable reaction resin and a cell growth stimulant.

Fig. 1

Fig. 2

Fig.3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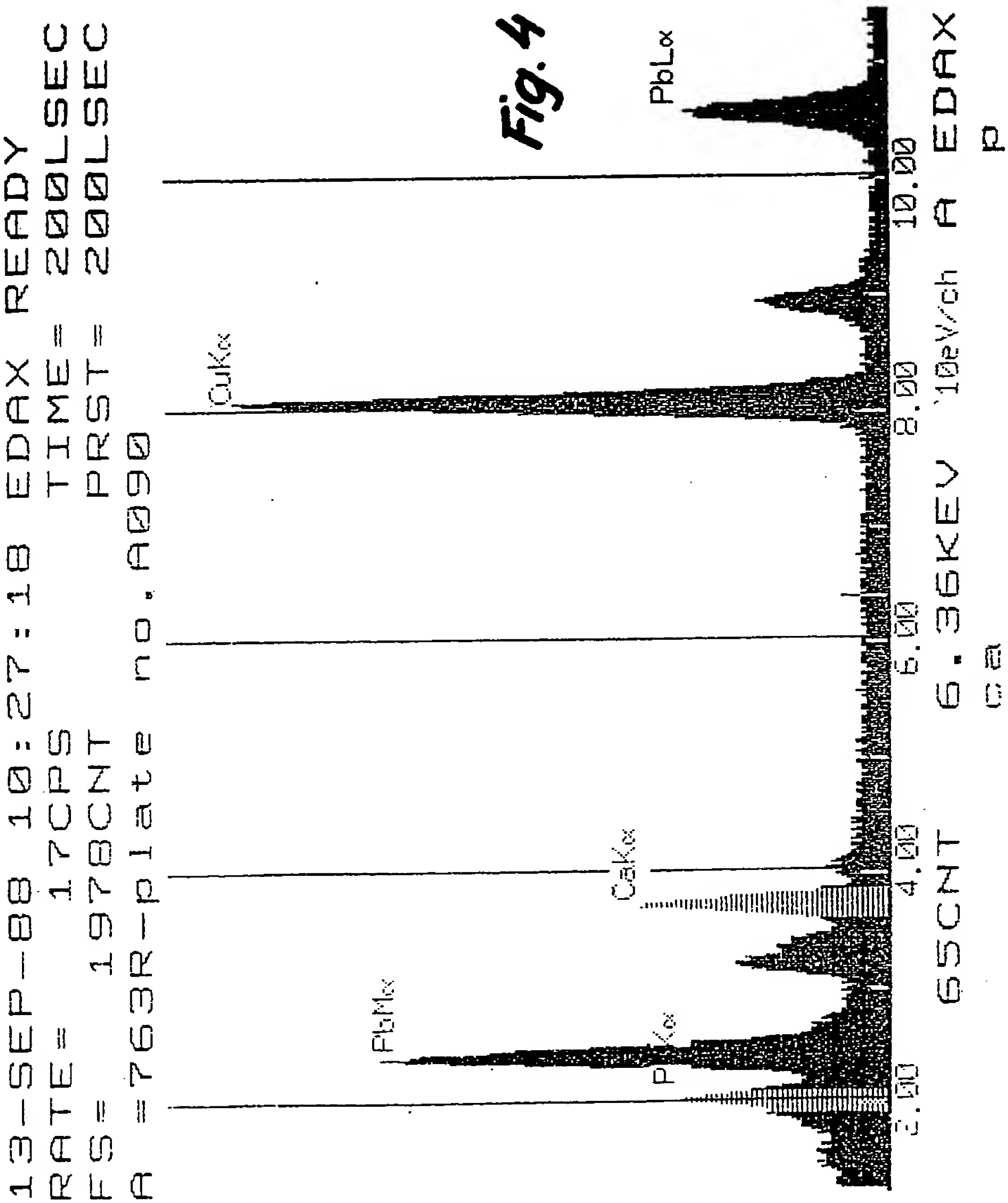
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Fig. 4